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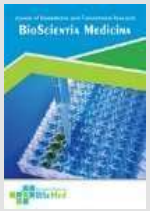

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The Role of Tecovirimat in the Management of Monkeypox

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A B S T R A C T

Monkeypox is a self-limited disease with symptoms that disappear within 14 to 21 days. Clinical management of monkeypox includes general supportive care and the use of antivirals that have activity against the monkeypox virus. This literature study aims to describe the role of tecovirimat in the management of monkeypox. Tecovirimat is an antiviral drug approved by the U.S. Food and Drug Administration (FDA) as part of the treatment management of smallpox in adults and children. Evidence of the efficacy of tecovirimat as mpox therapy was obtained from animal studies, where tecovirimat reduced mortality rates, reduced duration of illness and viral shedding. Tecovirimat inhibits the vp37 viral protein encoded by the F13 gene of the variola virus. This protein is highly conserved in orthopoxviruses, allowing tecovirimat to have in vitro activity against several orthopoxviruses, including vaccinia, variola, cowpox, and monkeypox viruses. In conclusion, tecovirimat is used in monkeypox sufferers with severe clinical conditions (sepsis, encephalitis, extensive lesions, bleeding manifestations), patients at risk of experiencing severe clinical conditions (immunocompromised, pregnant or breastfeeding, history of psoriasis, varicella zoster infection) and patients with one or more complications.

1. Introduction

Monkeypox is a zoonotic viral infection caused by the virus monkeypox (a group of the genus *Orthopoxvirus* in the family *Poxviridae*) which causes a rash similar to smallpox.[1,2] However, person-to-person transmission outside of direct contact and the death rate in monkeypox cases are much lower than in smallpox cases.[3] Clinical management of monkeypox includes general supportive care and the use of antivirals that have activity against the monkeypox virus (MPXV).

Currently, there are no antivirals approved specifically for MPXV infections.[4-6] Antiviruses developed for use in smallpox have proven useful against mpox.[7-10] One antiviral agent that has received WHO approval is tecovirimat. Tecovirimat works by inhibiting the orthopoxvirus protein which is important for the spread of the virus in its host.[7,8] This literature study aims to describe the role of tecovirimat in the management of monkeypox.

Monkeypox and its management

Monkeypox is a self-limited disease with symptoms that will disappear within 14 to 21 days. Until now there is no specific therapy or vaccine available for the infection monkeypox, but monkeypox outbreaks can be controlled with vaccination smallpox. Vaccination against smallpox It has been proven to prevent the

disease 85% of the time, but the vaccine has long been unavailable to the public after the global eradication of smallpox.[11,12]

Clinical management of monkeypox includes general supportive care and the use of antivirals that have activity against the monkeypox virus. About half of patients during the 2022 outbreak required pain medication (e.g., for oral or anogenital lesions). Additionally, stool softeners and topical lidocaine have been used for the treatment of proctitis. Warm baths and oral antihistamines have been shown to be beneficial in the treatment of pruritus. Supportive care that requires catheterization can be given to people who are dehydrated or at risk of dehydration, people who need more intensive pain management, and people with serious illnesses or complications.[7,8]

Patients with extensive anogenital ulcers or abscesses require drainage, debridement, and wound management. Antibiotics are prescribed for secondary bacterial infections. The effectiveness of any antiviral agent against monkeypox infection has not been evaluated in randomized or non-randomized trials. Three antiviral drugs, such as tecovirimat (intravenous and oral), cidofovir (intravenous and topical), and brincidofovir (oral) are potential options for treating monkeypox. This antiviral is approved for the treatment of smallpox based on animal models and safety data in healthy individuals which is expected to be effective for monkeypox as well.[3]

The agent of choice for the treatment of monkeypox is tecovirimat which is recommended in certain patients with severe disease (e.g. eye infection, encephalitis, severe proctitis, or pharyngitis) or those at risk of severe disease (patients with a compromised immune system or children under 8 years), patients with atopic dermatitis, pregnant, and breastfeeding mothers.[4] Early initiation and extended therapy should be considered in patients with weakened immune systems, including people living with HIV with CD4 <200, post-solid organ transplant patients, or with hematological malignancies.

Tecovirimat inhibits orthopoxvirus proteins that are important for spread in infected hosts. Randomized controlled studies in humans regarding the effectiveness of tecovirimat do not currently exist. Tecovirimat improves survival in animals suffering from monkeypox. In animal models of monkeypox, the drug was well tolerated and the most frequently reported side effects were headache, nausea, and abdominal pain, although the side effect profile was similar to placebo in a trial involving 360 healthy volunteers. Tecovirimat appears to be effective in vitro against the monkeypox virus lineage causing the 2022 outbreak. However, genotypic and phenotypic cases of resistance have been reported and alternative drugs should be considered in patients who do not respond to tecovirimat; that is, lesions or complications continue to develop after 14 days of treatment.[7]

Tecovirimat drug profile

Tecovirimat is an antiviral drug approved by the US FDA as part of the treatment for smallpox in adults and children. Smallpox is a disease caused by the variola virus, a member of the orthopoxvirus group of viruses. Since 1980, smallpox is thought to have been eradicated throughout the world. Although tecovirimat is only approved for the treatment of smallpox, it can also be used to treat other types of orthopoxvirus infections, including mpox. Tecovirimat can be used for the treatment of mpox through expanded access programs or through clinical trials.[15]

Tecovirimat (also known as TPOXX or ST-246) was the first antiviral indicated for the treatment of smallpox in adults and children. In 2018 the FDA approved tecovirimat as an antiviral drug in the management of smallpox. The use of tecovirimat in the management of other orthopoxvirus infections such as mpox is still ongoing and unapproved to date. Evidence of the efficacy of tecovirimat as mpox therapy was obtained from animal studies, where tecovirimat reduced mortality rates, reduced duration of illness, and viral shedding. Before the mpox outbreak in 2022, tecovirimat had been used in children aged 28 months and no side effects were found due to the use of tecovirimat, but there had been no clinical studies in children.[15]

Tecovirimat is an antiviral drug specifically for orthopoxvirus. Tecovirimat works by inhibiting the activity of the orthopoxvirus envelope protein VP37 (which is highly conserved in all orthopoxviruses), tecovirimat blocks its interaction with Rab9 GTPase and TIP47 (Rab9 specific effector protein). These conditions can prevent the formation of egress-competent enveloped virions that are essential for viral spread in the host. In particular, the results of in vitro studies indicate that the target of the antiviral activity of tecovirimat in cowpox virus is the product of the V061 gene.[15]

Tecovirimat demonstrated effectiveness in protecting several animal models of orthopoxvirus infection. Resistance to tecovirimat can develop through drug selection (as the drug has a relatively low resistance barrier as well as large reductions in antiviral activity can be caused by certain amino acid substitutions in the VP37 envelope protein). Tecovirimat resistance should be considered in patients who do not respond to treatment or whose disease recurs after an initial period of response.[16]

Tecovirimat is a CYP3A4 inducer and a weak CYP2C8 and CYP2C19 inhibitor, although its effects on most substrates of these enzymes are not thought to be clinically relevant. Additionally, no clinically relevant drug interactions were seen when tecovirimat was coadministered with bupropion, furbiprofen, or omeprazole. In healthy volunteers, coadministration of tecovirimat and repaglinide was associated with mild or moderate hypoglycemia, with symptoms resolving after food and/or oral glucose intake, and coadministration of tecovirimat and midazolam was associated with decreased midazolam concentrations.[15]

Monitoring blood glucose levels and hypoglycemic symptoms is recommended when administered with repaglinide and tecovirimat, as is monitoring the effectiveness of midazolam when administered with tecovirimat. No vaccine-drug interaction studies have been conducted in humans. Animal studies have shown that coadministration of tecovirimat and live smallpox vaccine (vaccinia virus) can reduce the immune response to the vaccine; whether this interaction has a clinical impact on vaccine effectiveness is unknown.[15]

The role of tecovirimat in the management of monkeypox

Tecovirimat is an antiviral drug approved for the treatment of smallpox. The effectiveness of tecovirimat in the management of smallpox has been established, with the drug having been approved based on studies in animal models using related orthopox viruses – specifically, non-human primates infected with monkeypox virus and rabbits infected with rabbit pox virus. Survival rates were much higher in animals receiving tecovirimat than in animals receiving a placebo.[16,17]

The US FDA and Health Canada also recently approved Tecovirimat to treat smallpox in 2018 and 2021. Most clinical studies have been conducted on the safety and pharmacokinetic parameters of Tecovirimat. Safety in humans was evaluated by assessing side effects in healthy volunteers receiving tecovirimat. The recommended dose of tecovirimat for the treatment of smallpox in humans was established by comparing plasma concentrations of the drug in healthy volunteers with those in animal models at doses that have been shown to be fully effective against monkeypox and rabbitpox. The recommended duration of therapy in humans is also based on research findings in animals and healthy people. Unlike smallpox, monkeypox remains endemic in some parts of the world (especially in West and Central Africa), and researchers can design clinical trials that are ethical and feasible.[16]

Tecovirimat inhibits the vp37 viral protein encoded by the F13 gene of the variola virus. This protein is highly conserved in orthopoxviruses, allowing tecovirimat to have in vitro activity against several orthopoxviruses, including vaccinia, variola, cowpox, and monkeypox viruses. The vp37 protein is involved in the final step of viral maturation and is required for the intracellular mature virus (IMV) to form an intracellular enveloped virus (IEV). The intracellular

enveloped virus then fuses with the cytoplasmic membrane to release virions for dissemination from the site of infection. The p37 protein is specific for the orthopoxvirus family, making tecovirimat highly selective in its inability to inhibit replication of other classes of viruses, including herpesviruses (Figure 1).[18]

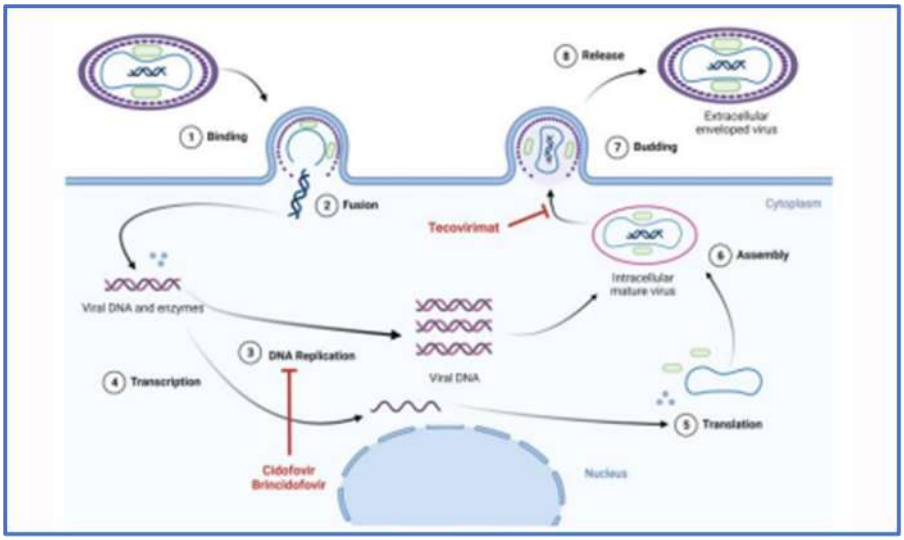

Figure 1. MPXV virus life cycle and the mechanism of action of tecovirimat.

Tecovirimat has been developed under the animal rule, which does not require effectiveness-based clinical trials in humans for life-threatening, unnatural, and severe diseases. Study of drug-drug interactions, drug-disease interactions, and drug-food interactions are important parameters regarding the safety and efficacy of a drug. Interactions of Tecovirimat with repaglinide and midazolam are known. Contraindications for Tecovirimat injection in patients with renal injury have also been reported.[19]

Tecovirimat has not shown teratogenic effects in mice but has shown non-teratogenic side effects in rabbits. Many patients were prescribed tecovirimat for lesions in anatomical areas that might result in serious sequelae, and nearly all received tecovirimat as an outpatient, suggesting that severe disease is rare. Improper use of the antiviral agent tecovirimat can potentially cause resistance.[20]

As of August 17th, 2022, the District of Columbia has reported 350 PCR-confirmed cases of monkeypox and has the highest per capita case rate in the United States. Of the case patients, 69% were between 25 and 39 years old, and 98% identified as male, 48% as white, and 37% as black. Most patients have a mild course of the disease and resolve on their own, but some patients have severe local manifestations, including proctitis. Both patients with severe monkeypox proctitis experienced a rapid reduction of anal pain after starting oral tecovirimat.[19,20]

2. Conclusion

Tecovirimat is used in monkeypox sufferers with severe clinical conditions (sepsis, encephalitis, extensive lesions, bleeding manifestations), patients who are at risk of experiencing severe clinical conditions (immunocompromised, pregnant or breastfeeding, history of psoriasis, varicella zoster infection) and patients with one or more complications. In theory, the mechanism of action of tecovirimat is to inhibit the VP37 protein which is useful in forming the envelope of the MPX virus. Tecovirimat 600mg given for 14 days has good efficacy in managing monkeypox cases.

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